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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,568	DUECKER, KLAUS	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-9 and 11) drawn to a method of producing a polypeptide and a method for screening to identify compounds that stimulate or inhibit the function or level of a polypeptide in Paper No. 7 (3 January 2003) is acknowledged. The traversal is on the ground(s) that it would not present a search burden to examine the addition group of an antibody specific for a polypeptide. This is not found persuasive because the antibody invention differs in search criteria and classification thus examination is not co-extensive. Claim 10 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7 (3 January 2003). The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment of Paper No. (15 February 2002) has been received and entered in full. Claim10 is withdrawn from consideration as discussed above, claims 7, 8, and 10 have been amended, and claims 1-9 and 11 are under examination.

3. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Specification

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pp. 13 line 13; pp. 24 line 7). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

6. Claims 1, 7, and 8 are objected to because of the following informalities: missing space between words "thesequence". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-9 and 11 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well-established utility.

8. The claims are directed to isolated polynucleotide comprising the nucleic acid of SEQ ID NO: 1, a method of producing an isolated polypeptide comprising SEQ ID NO: 2, and a method of identifying compounds which stimulate or inhibit the function or level of said polypeptide. The specification discloses the polynucleotide SEQ ID NO: 1 which encodes the polypeptide SEQ ID NO: 2. The specification asserts that the polypeptide encoded by SEQ ID NO: 1 is a novel G-protein coupled receptor (GPCR) that shares homology and/or structural similarity to GPCR_LYMST [Tensen et al. (1994) Proc. Natl. Acad. Sci. U.S.A. 91: 4816-4829 (**IDS**)]. GPCR are a gene superfamily known in the art to be expressed on the surface of many cell types and to encompass a massive receptor family. Gurrath [(2001) "Peptide-Binding G Protein-Coupled Receptors: New Opportunities for Drug Design" Current Medicinal Chemistry 8(13): 1605-1648] teaches that the GPCR superfamily constitutes the largest receptor family known. It is estimated that as many as 5000 distinct GFPR genes exist in the human genome. In addition, over 100 GPCRs are known with no characterized ligands and unknown physiological relevance (pp. 1606). Gurrath (2001) also teaches that all GPCRs are transmembrane receptors with a characteristic 7 transmembrane domain (TMD) motif, also known as "serpentine receptors", and all GPCRs work via a three-subunit effector system (pp. 1607; Figure 2). The state of the art holds that GPCRs fall into one of three major homology families for mammalian GPCRs: Family 1 (rho-family), Family 2 (scr-family), and Family 3 (metabotropic glutamate receptors) (pp. 1608-1609; Figure 4). Gurrath (2001) also teaches that GPCRs respond to a variety of agonists including but not limited to divalent cations, biogenic amines, fragrances, taste molecules, single amino acids, cannabinoids, prostaglandins, oligopeptides, globular proteins, chemokines, interleukins, neurotransmitters, and proteolytic enzymes (pp. 1609-1610; Table 1). The

specification does not disclose any data for any activity for the polypeptides encoded by SEQ ID NO: 1. There are no working examples.

9. There are no well-established utilities for newly discovered biological molecules. However, the specification contains several assertions of utilities. Each will be discussed in turn.

a. *The polynucleotide of SEQ ID NO: 1 encodes a novel G-protein coupled receptor:* The Applicant's assertion that SEQ ID NO: 1 encodes a GPCR is credible because it shares sequence homology with several GPCRs (including but not limited to LCR4, 6, and 7; WO 99/48921). However, this assertion is not specific, as the art recognizes a large number of GPCRs nor is it substantial. Firstly, it is not clear from the specification or the claims to which GPCR is claimed, what tissues are it expressed in, and at what levels. Hsu et al. [(2000) "The Three Subfamilies of Leucine-Rich Repeat-Containing G Protein-Coupled Receptors (LGR): Identification of LGR6 and LGR7 and the Signaling Mechanism for LGR7." Molecular Endocrinology 14(8): 1257-1271] teaches that a single GPCR, LGR7 (to which SEQ ID NO: 2 shares 92.7% homology, see SEQ Search Results #6) is expressed in many tissues including testis, ovary, oviduct, uterus, thymus, small intestine, colon, kidney, adrenal glands, brain and heart (pp. 1261; Figure 4). It is noted that Hsu et al. (2000) performed binding and functional assays to confirm the identity of their putative GPCRs (pp. 1268-1269; Figure 6; Table 1). Secondly, the specification's assertion that SEQ ID NO: 1 encodes a novel GPCR is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what SEQ ID NO: 1's properties are. For instance, US 6383778 claims a novel taste transduction GPCR and includes a functional assay with controls to

demonstrate that the claimed polypeptide is a working GPCR (Claims 1-11; Col. 9 lines 25-37; Example II).

b. *The polypeptide encoded (SEQ ID NO: 2) by SEQ ID NO: 1 GPCR biological activity:* The specification asserts that SEQ ID NO: 1 encodes a polypeptide that is a GPCR, which based on its structural similarity to prior art of GPCR polypeptides that have been characterized. While this assertion is credible it is neither specific nor substantial. It is not specific because this assertion would not have been accepted by one skilled in the art because the art establishes that GPCRs, while structurally similar, are functionally diverse. It is not substantial because of the lack of a working example of GPCR functional activity. The art teaches that using known and functionally established clones of GPCRs can yield genes of varying sequence homology. For instance, Howard et al. [(2001) "Orphan G-protein-coupled receptors and natural ligand discovery." TRENDS in Pharmacological Sciences 22(3): 132-140] teaches that the family of GPCR shares 7 TMD, and extracellular N-terminal domains, and intracellular-C-terminal domains with several conserved structural motifs. Despite this conservation of structural motifs, GPCRs usually only share ~45% sequence identity with one another. Furthermore, sequence homology is not indicative of which physiologically relevant ligands are active with a particular GPCR (pp. 132; Table 2). The assertion that SEQ ID NO: 1 encodes a GPCR is not substantial because the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For instance, Hsu et al. [(2000) "The Three Subfamilies of Leucine-Rich Repeat-Containing G Protein-Coupled Receptors (LGR): Identification of LGR6

and LGR7 and the Signaling Mechanism for LGR7." Molecular Endocrinology 14(8): 1257-1271] used sequence homology to identify and isolate putative GPCRs of the Leucine-Rich Repeat-Containing GPCR family (LCR GPCR). Despite being isolated from human cDNA libraries LGR7 shared the greatest homology with snail LGR at 33% compared to 24% for mammalian GPCRs (pp. 1268; Figure 1-2). Sequence homology is not a reliable as the sole basis upon which to establish biological activity. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remarks that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in

nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. In any case, the art clearly shows that structural similarity of different GPCRs is not predictive of expression patterns or functional similarity [Howard et al. 2001) Table 2]. For instance, Hsu et al. [(2000) "The Three Subfamilies of Leucine-Rich Repeat-Containing G Protein-Coupled Receptors (LGR): Identification of LGR6 and LGR7 and the Signaling Mechanism for LGR7." Molecular Endocrinology 14(8): 1257-1271] teaches that mutations of LGR7 designated LGR7(1) D637Y and LGR7(2) D603Y are "gain-of-function" mutants. Instead of the point mutations ablating activity, the aforementioned mutations created constitutively active GPCRs (pp. 1261-1262; Figure 6). Therefore, the specification's assertion that SEQ ID NO: 1 encodes a polypeptide with GPCR activity is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what those activities are due the differences in sequence.

c. *The polynucleotide (SEQ ID NO: 1) can be used to make polypeptides (SEQ ID NO: 2) for analysis, characterization, or therapeutic uses:* This asserted utility is not substantial nor specific. In recombinately expressing a polypeptide, the polynucleotide is transfected into a host cell and then the protein is recovered. However, the instant specification does not disclose any known function for the claimed polypeptide (SEQ ID

NO: 2) or any disease state, toxin, or poison associated with the claimed polynucleotide (SEQ ID NO: 1). In addition, this utility assertion is not specific as it can be applied to any given polynucleotide. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

d. *The polynucleotide SEQ ID NO: 1 has therapeutic uses:* This asserted utility is also not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1. Therefore, it is not clear how the skilled artisan would use the polynucleotide for therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

e. *The polynucleotide is useful as a probe or primer:* The specification asserts that SEQ ID NO: 2 is useful as a probe to detect genes encoding SEQ ID NO: 2 or variants thereof, as primers to amplify corresponding gene fragments, to identify potential genetic disorders, in sequence arrays, to screen collections of genetic material from patients who have a particular medical condition, restriction fragment length polymorphism (RFLP) screens, to search sequence databases, to identify mutations associated with a particular disease, or in anti-sense technology to regulate gene expression of SEQ ID NO: 1. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the nucleic acid probes to identify such. It would take significant further research to

determine if the polynucleotide could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used as probes or primers, this asserted utility is not specific.

f. *The polynucleotide (SEQ ID NO: 1) can be used to make chimeric proteins:* This asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use a chimeric polypeptide for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the identified chimeric polypeptide, the asserted utility is not substantial.

g. *The polynucleotide (SEQ ID NO: 1) can be used in chromosome mapping:* In order to be useful as a chromosomal probe, the precise chromosomal map position must be disclosed. The art suggests that the GPCR isoforms are members of a larger gene superfamily. For instance, WO 99/48921 teaches the localization of LGR4 to human chromosome 5q34-35 and 12q15 for LGR5 (pp. 25 Example 4). Furthermore, Hsu et al. [(2000) "The Three Subfamilies of Leucine-Rich Repeat-Containing G Protein-Coupled Receptors (LGR): Identification of LGR6 and LGR7 and the Signaling Mechanism for LGR7." Molecular Endocrinology 14(8): 1257-1271] teaches that LGR6 and LGR7 are located on chromosome 1q32 and 4q32 respectively (pp. 1261; Figure 5). Thus, even closely related isoforms from the same family can be located on different chromosomes altogether. Substantial further research would be required for the skilled artisan to

determine where this particular sequence is mapped in order to use the nucleic acid molecule in the asserted utility as a chromosomal map probe. The asserted utility is also not specific, since the entire class of genes can be asserted to be used in this way.

h. *The polynucleotide is useful for encoding antigenic portions of SEQ ID NO: 2:* This utility is also not substantial, because there is no substantial utility for the full-length polypeptide. If substantial further research is required to determine how to use the full-length polypeptide, then substantial further research is also required to determine how to use antibodies generated from antigenic fragments.

i. *The polynucleotide is useful for making transgenic animals:* No phenotype has been disclosed for such transgenic animals. In the absence of such disclosure, the skilled artisan would have to experiment significantly in order to determine how the transgenic animals could be used. Therefore, the asserted utility is not substantial.

j. *The polypeptide encoded by SEQ ID NO: 1 do not have a known ligand:* The specification does not identify any specific ligands for the claimed novel GPCR. In respect to GPCRs, Kenakin [(2002) "Drug Efficacy at G Protein-Coupled Receptors" Annu. Rev. Pharmacol. Toxicol. 42: 349-379] teaches their binding and response to specific ligands (agonists) is variable, as are the effects on the receptor. In addition, receptor behavior involves several reactions including but not limited to internalization, pleiotropic interaction with multiple G-proteins, desensitization, oligomerization, and interaction with membrane auxiliary proteins (pp. 357; 362-367; Figure 1-4). Further, as noted above by Gurrath (2001) and Howard et al. (2001) possible GPCR ligands cover a huge range of bioactive molecules including but not limited to light, Ca^{2+}, odorants,

amino acids, nucleotides, peptides, fatty acid derivatives, and polypeptide ligands (pp. 132). A skilled artisan would have had to experiment significantly to identify any allergy, disease, or disorder associated with SEQ ID NO: 2. Therefore, the asserted utility is not substantial. The asserted utility is also not specific, since all receptors can be used to screen for ligands.

k. *SEQ ID NO: 2 can be used in assays for drug screening to identify compounds that modulate secreted protein expression:* This asserted utility is also not substantial. In such assays, compounds are screened for their ability to up-regulate or down-regulate activity of SEQ ID NO: 2. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 2 expression levels or forms (i.e., mutations). Therefore, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial.

l. *SEQ ID NO: 2 can be used in assays for screening to identify receptors:* This asserted utility is also not substantial. In such assays, polypeptides are screened for their ability to bind compounds similar to ligands that bind SEQ ID NO: 2. However, the instant specification does not disclose any specific ligand for SEQ ID NO: 2. Therefore, it is not clear how the skilled artisan would use a potential receptor identified by this method. Since significant further research would be required to determine how to use the identified potential receptors, the asserted utility is not substantial.

m. *SEQ ID NO: 2 is useful as a probe:* The specification asserts that SEQ ID NO: 2 is useful as probes to detect genes or variants thereof, to identify potential genetic disorders, or to regulate expression of SEQ ID NO: 2. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the polypeptide, there is also no substantial utility for the probes to identify SEQ ID NO: 2 in tissues or biological samples. It would take significant further research to determine if the instantly claimed novel GPCR could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 2 expression levels or form (i.e., mutations) has been disclosed in the specification. Also, all polypeptides can be used as "probes" to detect the genes encoding them, thus the asserted utility is not specific.

n. *SEQ ID NO: 2 can be used in drug design:* This asserted utility is not substantial. In such design paradigms, compounds are screened for their ability to up-regulate or down-regulate expression of the polypeptide or its activity. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 2 expression levels or forms (i.e., mutations) or activity. In addition, this utility assertion is not specific as it can be applied to any given polypeptide. Therefore, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial.

o. *The polypeptide (SEQ ID NO: 2) may exhibit immune stimulating activity for use as a vaccine*: Neither the specification nor the art discloses any evidence to show that SEQ ID NO: 2 has immune stimulating activities. A skilled artisan would have had to experiment significantly to identify and characterize any presumed immune stimulating activity for SEQ ID NO: 2. Therefore, the asserted utility is not substantial.

p. *The polypeptide (SEQ ID NO: 2) may be useful in therapy*: Neither the specification nor the art discloses any evidence to show that SEQ ID NO: 2 has any relation or involvement in a known disease or disorder. A skilled artisan would have had to experiment significantly to identify and characterize any presumed use or role in a particular disease/disorder and the subsequent therapy for SEQ ID NO: 2. Therefore, the asserted utility is not substantial.

10. Therefore, in the absence of a well-established utility, and the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 U.S.C. § 101.

If Applicant can submit evidence (in the form of a declaration under 37 CFR 1.132 or post-filing date publications) supporting the specification's assertion that SEQ ID NO: 2 has a specific function similar to a known G-protein coupled receptor (GPCR), wherein the specific function was predicted by the specification as originally filed, such would be viewed favorably as evidence of patentable utility.

11. Claims 1-9 and 11 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted

utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore regarding derivatives and fragments of SEQ ID NO: 2 polypeptides, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary

artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1): 34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

12. Claims 1, 4, 5, 6, 7, 8, 9, and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not contain a written description of variants and fragments of the claimed GPCR.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of SEQ ID NO: 2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

13. Claims 1, 4, 6, 7, 8, 9, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 4, 7, and 8 use the phrase, "fragments and variants"—not clearly claimed as singular and alternative. It is not clear whether or not multiple

fragments and/or variants are contemplated. To obviate this rejection, the Applicant may amend the claims to read "a fragment or a variant thereof".

Regarding claims 1, 7, 8, and 9, SEQ ID NO: 1 has 6 reading frames. The claims are directed to a polypeptide encoded by SEQ ID NO: 1, it is not clear which reading frame is claimed as the present invention.

Claim 6 recites the limitation "said expression vector" in the second line. There is insufficient antecedent basis for this limitation in the claim.

Claims 7 and 8 recite the limitation "the polypeptide of an isolated polypeptide". It is not clear what is meant by this phrase in terms of defining the claimed invention.

In claim 11, it is not clear how part(f) relates to the goal of the preamble of claim 11. It is not clear what result must be obtained in any of the methods (a)-(f) to identify a compound as a stimulator or inhibitor.

The term "stringent" in claim 4 is a relative term which renders the claim indefinite. The term "stringent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 4, 6, 7, 8, 9, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5756309 (26 May 1998). Claims 1-28 of US 5756309 recite the limitations of an isolated polynucleotide, recombinant vectors, and methods of making a polypeptide encoded by said polynucleotide for a GPCR (claims 1-28). Since the instant application does not recite any structural limitations for "(e) fragments and variants of such polypeptides in (a) to (d)" for claim 1, US 5756309 meets the limitations of claims 1, 4, 6, 7, 8, and 9. US 5756309 also discloses a method of using the claimed polynucleotides and recombinant cells in a screening assay thus meeting the limitations of claim 11 (Col. 28-30).

15. Thus claims 1, 4, 6, 7, 8, 9, and 11 are anticipated by the prior art.

Summary

16. Claims 1-9 and 11 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elyabeth C. Kemmerer

CJN
February 24th, 2003